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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/54

A1

(11) International Publication Number: WO 99/45929

(43) International Publication Date: 16 September 1999 (16.09.99)

(21) International Application Number: PCT/US99/02159

(22) International Filing Date: 1 February 1999 (01.02.99)

(30) Priority Data:
09/036,960 9 March 1998 (09.03.98) US

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(81) Designated States: AU, BR, CA, CN, JP, KR, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: THE TREATMENT OF RETINAL EDEMA WITH BRINZOLAMIDE

(57) Abstract

Methods for preventing and treating retinal edema with brinzolamide are disclosed.

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IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

THE TREATMENT OF RETINAL EDEMA WITH BRINZOLAMIDE

The present invention is directed to the use of brinzolamide to treat retinal edema.

Background of the Invention

In 1977, Miller, et al., did studies with bullfrogs and found that the pigment epithelium actively secretes sodium and calcium into the retinal space and absorbs chlorine and perhaps bicarbonate and potassium, and that this activity could be important in controlling the ionic milieu in the outer retina. Miller, et al., "Active Transport of Ions Across Frog Retinal Pigment Epithelium," *Experimental Eye Research*, 25:235-248 (1977).

In 1982, Marmor, et al. suggested that acetazolamide (intravenous) might have application in preventing or slowing the spread of retinal detachments or hasten resorption of subretinal fluid. Marmor, et al., "Enhancement of Retinal Adhesion and Subretinal Fluid Resorption by Acetazolamide," Investigative Ophthalmology, 23 (1):121-124 (July, 1982). In 1986, it was found that acetazolamide in high doses enhanced subretinal fluid resorption, but had little effect when dosed as ordinarily used. Marmor, et al., "Pharmacologic Modification of Subretinal Fluid Absorption in the Rabbit Eye," *Archives of Ophthalmology*, 104:1674-1677 (Nov. 1986). Clinical studies in 1988 showed that acetazolamide modifies or causes resolution of macular edema in some patients. The studies showed no detectable effect on macular edema due to primary retinal vascular disease in contrast to the macular edema resulting from inflammation or inherited outer retinal disorders. Cox, et al, "Treatment of Chronic Macular Edema With Acetazolamide," *Archives of Ophthalmology*, 106:1190-1194 (September 1988). In 1994, Borhani et al., suggested the intraocular administration (injection) of acetazolamide for treating cystoid macular edema rather that systemic administration due to the serious systemic side effects associated with systemic administration. Borhani, et al., "Vitreoretinal Toxicity of Acetazolamide Following Intravitreal Administration in the Rabbit Eye," *Ophthalmic Surgery*, 25 (3):166-169 (March 1994).

Brinzolamide is disclosed in commonly assigned U. S. Patent Nos. 5,240,923 and 5,378,703 for its usefulness in controlling intraocular pressure, particularly in the

treatment of glaucoma. These patents are incorporated herein by reference.

Retinal edema is treated today with non-steroidal anti-inflammatories, corticosteroids, laser photocoagulation, and systemic acetazolamide. The use of brinzolamide provides an alternative drug for the treatment of this prevalent condition.

Summary of the Invention

The present invention is directed to the topical use of brinzolamide formulations to treat retinal edema.

Description of Preferred Embodiments

Retinal edema, including macular edema, also referred to as cystoid macular edema (CME) or cystic macular edema, may develop in association with a variety of ocular conditions. These conditions include, but are not limited to, diabetic retinopathy, ischemic retinopathies (e.g., vein occlusion), posterior segment inflammation, laser photocoagulation, and intraocular surgery, such as cataract removal. The edema is a result of cystic accumulation of extracellular interstitial fluid in the outer plexiform and inner nuclear layers as a result of the breakdown of the blood retinal barrier. The anatomy of the macular region of the retina predisposes it to the development of edema. The macula is a shallow concavity with a central depression, the fovea. The cells in the macular region have a high metabolic activity and the thickness of the outer plexiform layer forms a reservoir for the potential accumulation of extracellular fluid. The central avascular zone creates a watershed arrangement between the choroidal and retinal circulation.

Normally, the accumulation of fluids is prevented by tight junctions joining the endothelium of retinal capillaries creating a "blood-retinal" barrier. In addition, an intact functional retinal pigment epithelium (RPE) also prevents fluids from reaching the inner retina by tight junctions and active transport. Thus, the accumulation of extracellular intraretinal fluid is prevented by osmotic forces, hydrostatic forces, capillary permeability, and tissue compliance, all of which ensure the capillary filtration is equal to the rate of fluid removal. Typically, edema occurs as a result of one or more of the following: (a) injury to the cellular components due to hypoxia or ischemia (cytotoxic edema), (b) primary breakdown in the blood brain barrier (vasogenic edema), and (c) decreased fluid resorption due to RPE dysfunction.

Brinzolamide, (R-(+)-4-ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno [3,2,e]1,2-thiazine-6-sulfonamide-1,1-dioxide, is a carbonic anhydrase inhibitor which has been found to be effective in lowering the elevated intraocular pressure associated with intraocular hypertension and glaucoma, but surprisingly, we have found that brinzolamide is well-suited to penetrate into the retina, choroid, and optic nerve head upon topical ocular administration and is effective in preventing and/or reducing retinal edema.

Brinzolamide can be administered topically to the eye, systemically (250-1000 mg/day), or via intravitreal (0.1-10 mg/eye), or periocular (0.1-50 mg/eye) injections. In order to prevent the edema associated with laser photocoagulation, it is preferrable to administer brinzolamide prior to and/or following the laser procedure.

Brinzolamide is preferably formulated as a topical ophthalmic suspension with a pH of about 4.5-7.8. It will normally be contained in the formulation at a concentration of 0.005-10% by weight, preferably 0.25% to 5.0% by weight. Thus, for topical presentation, one to three drops of these formulations will be delivered to the surface of the eye one to four times a day according to the routine discretion of a skilled clinician.

The following example is the preferred formulation for use according to the present invention:

Example

Ingredient	Percent w/v
Brinzolamide	1.0
Mannitol	3.3
Carbopol 974P	0.4
Tyloxapol	0.025
Disodium EDTA	0.01
Benzalkonium Chloride	0.01 + 5% excess
Sodium Chloride	0.25
Sodium Hydroxide/Hydrochloric Acid	pH 7.5
Purified Water	QS 100

We Claim:

1. A method for treating or preventing retinal edema which comprises administering a pharmaceutically effective amount of brinzolamide.

2. The method of Claim 1 wherein the brinzolamide is administered systemically, topically to the eye, or via intraocular or periocular injection.

3. The method of Claim 2 wherein the brinzolamide is administered topically to the eye.

4. The method of Claim 3 wherein the brinzolamide is administered at a concentration of 0.005-10 percent by weight.

5. The method of Claim 4 wherein the brinzolamide concentration is 0.25-5.0 percent by weight.

INTERNATIONAL SEARCH REPORT

Ir. ...ational Application No
PCT/US 99/02159

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 00133 A (MERCK & CO INC ;SUGRUE MICHAEL S (US)) 7 January 1999 see abstract see page 2, line 24 - line 31; claims 1-5	1-5
X	WO 97 30704 A (MERCK & CO INC ;INDIANA UNIVERSITY FOUNDATION (US); AMON FELIX W () 28 August 1997 see abstract see page 3, last paragraph see page 4, paragraph 1 see page 8, last paragraph - page 9, paragraph 2; claims 1,4,7,10	1-5
A	US 5 153 192 A (DEAN THOMAS R ET AL) 6 October 1992 see column 1, line 55 - line 59; table 1	1-5

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 June 1999	15/07/1999

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 91 15486 A (ALCON LAB INC) 17 October 1991 see abstract see page 2, line 16 - line 19; claims; examples 16.2,19.2; table 1	1-5
Y	COX S N ET AL: "TREATMENT OF CHRONIC MACULAR EDEMA WITH ACETAZOLAMIDE" ARCHIVES OF OPHTHALMOLOGY, vol. 106, no. 9, 1 September 1988, pages 1190-1195, XP000197574 cited in the application see the whole document	1-5
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Y	SCHILLING H ET AL: "THERAPIE ZYSTOIDER UND DIFFUSER MAKULAOEDEME NACH UVEITIS UND KATARAKT-CHIRURGIE MIT DEM CARBOANHYDRASE-HEMMER ACETAZOLAMIDE (DIAMOX). ERGEBNISSE EINER PILOTSTUDIE. THERAPY OF CYSTOID AND DIFFUSE MACULAR EDEMA FOLLOWING UVEITIS AND CATARACT SURGERY WITH THE CARBONIC ANHYDRASE INHIBITOR ACETAZOLAMIDE" KLINISCHE MONATSBLAETTER FUER AUGENHEILKUNDE, vol. 202, no. 1, 1 January 1993, pages 206-211, XP000197567 see the whole document	1-5

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/02159

Box I Observations where certain claims were found unsearchabl (Continuation f item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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